REMARKS

Restriction Requirement

The examiner modified the outstanding restriction requirement by removing the restriction on the variable R^1. Group I is still elected, where Group I is now drawn to compounds and compositions of Formula I, where n is 1 and R^2 is benzyl. The compound of Example 1 remains the elected species.

Groups II and III are withdrawn. The withdrawn method of use Claims 19-22 have been amended so that they depend on Claim 23. They are now directed to methods of using compounds and compositions of Group I and are ready to be rejoined once the claims of Group I are allowed.

Claim Amendments

The claims have been amended as follows. The amendments address issues raised by the examiner and also bring the claims into conformance with the restriction requirement.

Claim 1 has been canceled and rewritten as new Claim 23. The variables in new Claim 23 are supported as follows:

- The definition of R^2 is taken from Claim 6. The definition in Claim 23 has been changed to benzyl, and includes benzyls having one or two methyl substituents on the methylene. These correspond to (C_{1-3}alkyl)-phenyl in Claim 6, where C_2alkyl and C_3alkyl are branched. This is further supported by the two R^2 groups listed in Claim 8, numbers (18) and (19).
- The definition of R^3 is taken from Claim 1. R^3 is defined as a heterocyle, in conformance with the restriction requirement. The list of substitutents on the heterocyclic group is also incorporated from Claim 1. Finally, "heterocyle" has been defined as a Markush group of heterocyles which are provided on pages 15-16 of the specification.
- The definition of R^5 is taken from Claim 16.
- The definition of R^4 as H is taken from Claim 14.

- R^6, R^9 and R^{10} are defined as H and a number of other variables in Claim 1. R^6 and R^{10} are always H in the examples. R^9 is also usually H. R^6, R^9 and R^{10} have been defined as H.
- The value of n has been defined as 1, as required by the restriction requirement.

The claims that were dependent on Claim 1 have been amended so that they now depend on Claim 23.

Claim 17, which claims the specific compounds in the examples by reference to the examples, has been canceled and rewritten as new Claim 24, which provides the structures of the examples.

Other changes in the claims eliminate non-elected subject matter or eliminate informalities and typographical errors.

Claim Rejections – 35 USC§112, second paragraph

Claim 17 is rejected for claiming compounds by reference to the specification. The Examples have been inserted into claim 17, which is written as new Claim 24. The rejection should be withdrawn.

Claim Rejections – 35 USC§112, first paragraph

Claims 1-18 are rejected under 35 USC§112, first paragraph for lack of enablement. The examiner's position is that the scope of the claims is not commensurate in scope with the disclosed examples.

The examiner inquires on pages 4-5 about the assay, which states that the compounds in the examples generally have an IC_{50} of less than about 1μM. The cutoff for selecting compounds based on the *in vitro* assay is 1μM, and the examples were selected based on the assay. The disclosed compounds therefore all bind to the receptor with an IC_{50} of less than 1μM. The words "generally" and "about" are used because measurement of IC_{50} can vary somewhat due to variations normally inherent in the assays and measurement methods.

With respect to the examiner's comments abut the table from the publication, Xia, et al at the bottom of page 5 of the Office Action, the examiner argues that minor structural changes can result in large changes in activity. This conclusion is based on one inactive compound out of the 13 that were tested for CCR2 binding activity. It is noteworthy that the other 12 compounds in the table are active. There is no requirement that every compound in a genus has to be active. A ratio of 12 active compounds to one inactive compound suggests that minor structural variations change the activity but do not generally result in inactive compounds.

The examiner also cites a publication by Pinkerton et al that shows that changes in the linker group can lead to large variations in activity in a series of CCR2 antagonists that are structurally somewhat similar to the series in the instant application. It is important to note that there is only one linker claimed in the instant application for the entire series of compounds. The only variations between the piperidine group on the left and the phenyl of the benzyl group on the right are the pendant R^1 substituent and the possible substitution of one or two CH_3 groups onto the methylene of the benzyl groups. These are minor compared with the changes that are disclosed in the Pinkerton et al. publication.

Finally, the examiner cites a publication by Yang, et al. in which the authors state that the bis-trifluoromethylbenzene group that is analogous to the phenyl group on the right hand side of the compounds of the pending application is very sensitive to changes in substituents, such as replacing the CF^3 groups.

Applicants wish to cite US2006-0116421 (Butora I), which was filed on the same date as the instant application and describes a class of compounds that have structural similarities to the compounds in the instant application. The compounds in the Butora I application are structurally more similar to those in the pending application than the compounds described in the publication by Yang et al. There are many examples in Butora I. Note that the compounds in Butora I were chosen because they have an IC_{50} of less than 1μM in the binding assay, as was the case with the current claims. Compounds that were selected as examples in the series of compounds in Butora I have a wide range of substitutions on the phenyl on the right side of the structure, as can be seen in Table 2 and also by reviewing the list of chemical structures in Claim 30. Compounds having a phenyl group substituted with substituents other than two trifluoromethyl groups are clearly also active.

Similarly, US 2005-0261325 (Butora II) also discloses CCR2 antagonists that have structural similarities to the compounds in the current application. These compounds were also selected based on IC_{50} values of less than 1 μM, and they have an analogous phenyl group on the right side of the structure. There are numerous examples in the Butora II application of active compounds that have substituents other than two CF_3 groups on the phenyl. These include Examples 18-4 to18-8, 34-37, 39, 40, 42, 45, and 93-97.

In summary, there is a reasonable expectation that a broader range of compounds than just the bis-trifluoromethylphenyl compounds will have activity in the compounds claimed in the current application. The claims have been amended so that they are significantly reduced in scope from the original claims. It is respectfully submitted that the scope of the amended claims is commensurate with the disclosure in view of what is provided in the application or is published elsewhere.

Conclusion

All of the grounds for rejection have been overcome. It is respectfully submitted that the claims are in condition for allowance. Such allowance is earnestly solicited.

If the examiner needs to discuss any matter relating to this application, the examiner is invited to telephone the undersigned attorney at the number below.

A fee is not believed to be required with this timely response. If any fee is required, the fee may be charged to Merck Deposit Account No. 13-2755.

Please also take note that an Information Disclosure Statement is included with this response. It cites 4 CCR2 applications that were filed by the same corporate applicant on the same day, including the two applications cited above to support broader diversity of substituent groups.

Respectfully submitted,

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